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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,307	12/07/2005	Andrew N Margioris	Q87992	3693

23373 7590 01/22/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
01/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,307	MARGIORIS ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1-3,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-10,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/7/05; 4/11/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group IV, claims 4-10, 13 and 14 (all in part), directed to pharmaceutical compositions and kits comprising CRH-R2 agonists in the reply filed on 2 November 2007 is acknowledged. Upon reconsideration, Group IV is rejoined with Group III, which reads on pharmaceutical compositions and kits comprising CRH-R1 antagonists. Claims 1-3 and 11-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2 November 2007.

Claims 4-10, 13 and 14 are under examination insomuch as they pertain to pharmaceutical compositions and kits comprising CRH-R2 agonists and CRH-R1 antagonists.

Claim Objections

Claim 4 and 13 objected to because of the following informalities: For the sake of clarity, CRH-R2 should be written out as corticotrophin releasing hormone receptor 2 and CRH-R1 as corticotrophin releasing hormone receptor 1 in the independent claims (4 and 13) followed by the abbreviation parenthetically. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph—Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-10, 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions and kits comprising CRH-R2 agonists and CRH-R1 antagonists that are known in the art, does not reasonably provide enablement for the claims as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The major issue in the instant case is breadth. The claims recite pharmaceutical compositions and kits comprising CRH-R2 agonists or CRH-R1 antagonists. The

definition of CRH-R2 agonists and CRH-R1 antagonists is extremely broad (see paragraph [0020]):

> Thus a "synthetic CRH-R1 antagonist" is a synthetic compound that inhibits CRH-R1 function and when added to a CRH-R1 assay blocks the effects of CRH peptides and the effects of synthetic CRH-R1 agonists, resulting in a smaller signal when the CRH-R1 receptor is stimulated with a agonist ligand therefore, such as CRH, compared with same assay but without said compound. A "synthetic CRH-R2 agonist" is a synthetic compound that activates CRH-R2 and in a CRH-R2 assay gives rise to a signal as a result of the CRH-R2 receptor activation, such as CRH, compared with same assay but without said compound.

Paragraph [0021] goes on to describe assays known in the art that may be used for determining suitable CRH-R2 agonists and CRH-R1 antagonists:

> CRH-R1 and CRH-R2 assays are known within the art. In principle any suitable CRH-R1 and CRH-R2 assays known within the art may be used for determining if a candidate synthetic compound is an antagonist or agonist respectively. Preferred examples of CRH-R1 and CRH-R2 assays have been developed. Assays for biological activity via the CRH-R1 receptor: (a) CRH activates p38 mitogen-activated protein kinase, stimulates Fas ligand production and induces apoptosis in PC12 rat pheochromocytoma cells. The CRH-R1 antagonist antalarmin blocks all these CRH-mediated effects)(Dermitzaki et al, 2002). (b) CRH enhances the inflammatory response to lipopolysaccharide (LPS) of macrophages in vitro. The enhancing effect of CRH is blocked completely by the CRH-R1 antagonist antalarmin (Agelaki et al, 2002). Assay for biological activity via the CRH-R2 receptor: Urocortin and Urocortin II induce apoptosis on macrophages. This effect is mediated by the CRH-R2 receptor since the specific antagonist sauvagine-30 completely abolishes this effect (Tsatsanis et al, submitted).

Thus the claims encompass not only CRH-R2 agonists and CRH-R1 antagonists known in the art, but those yet to be discovered, as evidenced by paragraph [0021]. The claims amount to single means claims. Single means claims are those that cover every conceivable means for achieving the stated purpose. Single means claims are

nonenabling for the scope of the claim because the specification discloses at most only those means known to the inventor, in this case, CRH-R2 agonists and CRH-R1 antagonists. When claims depend on a recited property, a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See MPEP 2164.08(a).

Due to the large quantity of experimentation necessary to discover all the CRH-R2 agonists and CRH-R1 antagonists encompassed by the claims, the lack of direction/guidance presented in the specification regarding and the absence of working examples directed to all of the agents encompassed by the claims and the breadth of the claims which fail to recite limitations on CRH-R2 agonists and CRH-R1 antagonists, which would require the person of skill in the art to undergo a discovery process to determine the agents encompassed by the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, first paragraph—Written Description

Claims 4-10 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of a CRH-R2 agonist or CRH-R1 antagonist. There is not even identification of any particular portion of the structure that must be conserved. Furthermore, the specification at paragraph [0021] describes methods for discovery of these agents, and provides only one example of a CRH-R1 antagonist, antalarmin. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus, which encompasses undiscovered CRH-R2 agonists or CRH-R1 antagonists.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). It is clear from paragraphs [0020] – [0022] of the instant specification that Applicants are not in possession of the claimed genus

With the exception of CRH-R2 agonists and CRH-R1 antagonists known in the art, the skilled artisan cannot envision the detailed chemical structure of the encompassed agents, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. ***Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it,*** as is disclosed at paragraphs [0020] - [0022] of the specification. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated CRH-R2 agonists and CRH-R1 antagonists known and documented in the art (in addition to antalarmin), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4-10 and 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Webster et al. (Endocrinol. 1996; 137: 5747-5750).

The claims are drawn to a pharmaceutical composition comprising one or more synthetic CRH-R1 antagonists and/or CRH-R2 agonists (claim 4); wherein said composition is formulated for local or systemic administration (claim 5); wherein said composition further comprises usual exhibients such as diluents, fillers, binders, disintegrants, lubricants, conserving agents, flavorings and colorings (claim 6), wherein said formulation is formulated for oral, parenteral or intradermal administration (claim 7), wherein said composition is formulated as an injection liquid (claim 8), the pharmaceutical composition according to claim 4, wherein the one or more synthetic CRH-R1 antagonist and/or CRH-R2 agonist comprises antalarmin (claim 9), the pharmaceutical composition according to claim 9, wherein the one of more synthetic CRH-R1 antagonist and/or CRH-R2 agonist is antalarmin (claim 10), a kit intended for the treatment of an inflammatory disease or condition comprising one or more CRH-R1 antagonists and/or CRH-R2 agonists comprised in one of more individual pharmaceutical compositions (claim 13) and the kit according to claim 13, wherein the one or more CRH-R1 antagonists and/or CRH-R2 agonists comprises antalarmin (claim 14).

Webster et al. teach administration of antalarmin and vehicle to rats via injection (see p. 5748, whole page). Since antalarmin was found to have an anxiolytic and anti-

inflammatory therapeutic effect (see abstract; p. 5750, left column, last 2 paragraphs), the usage taught in Webster is not inconsistent with pharmaceutical usage. Thus the limitations of claims 4, 5, 6, 7, 8, 9 and 10 are met by Webster et al. In addition, since measured amounts of antalarmin were administered to the rats (see Figure 1, p. 5748), the limitations of kits (claims 13-14) are also met. Thus claims 4-10 and 13-14 do not teach anything new over the prior art.

Claims 4-7, 9-10 and 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Habib et al. (PNAS, 2000; 97: 6079-6084).

The claims are drawn to a pharmaceutical composition comprising one or more synthetic CRH-R1 antagonists and/or CRH-R2 agonists (claim 4); wherein said composition is formulated for local or systemic administration (claim 5); wherein said composition further comprises usual exhibients such as diluents, fillers, binders, disintegrants, lubricants, conserving agents, flavorings and colorings (claim 6), wherein said formulation is formulated for oral, parenteral or intradermal administration (claim 7), the pharmaceutical composition according to claim 4, wherein the one or more synthetic CRH-R1 antagonist and/or CRH-R2 agonist comprises antalarmin (claim 9), the pharmaceutical composition according to claim 9, wherein the one of more synthetic CRH-R1 antagonist and/or CRH-R2 agonist is antalarmin (claim 10), a kit intended for the treatment of an inflammatory disease or condition comprising one or more CRH-R1 antagonists and/or CRH-R2 agonists comprised in one of more individual pharmaceutical compositions (claim 13) and the kit according to claim 13, wherein the

one or more CRH-R1 antagonists and/or CRH-R2 agonists comprises antalarmin (claim 14).

Habib teach oral administration of antalarmin (a CRH-R1 antagonist) dissolved in Primatreat banana flavored tablet form to primates (see p. 6080, left column, 3rd – 4th paragraphs), and since the antalrmin was found to have an anxiolytic therapeutic effect (see abstract; p. 6084, right column, last paragraph), this usage is consistent with pharmaceutical use, thus meeting the limitations of claims 4, 5, 6, 7, 9 and 10. Because the antalarmin was formulated for oral dosage, and measured amounts were given (see 6080, left column, 4th paragraph), the claims also meet the limitations of a kit (claims 13 and 14). Thus claims 4-7, 9-10 and 13-14 do not teach anything new over the prior art.

Claims 4-8 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Wei et al. (Peptides, 1998; 19: 1183-1190).

The claims are drawn to a pharmaceutical composition comprising one or more synthetic CRH-R1 antagonists and/or CRH-R2 agonists (claim 4); wherein said composition is formulated for local or systemic administration (claim 5); wherein said composition further comprises usual exhibients such as diluents, fillers, binders, disintegrants, lubricants, conserving agents, flavorings and colorings (claim 6), wherein said formulation is formulated for oral, parenteral or intradermal administration (claim 7), wherein said composition is formulated as an injection liquid (claim 8), and a kit intended for the treatment of an inflammatory disease or condition comprising one or

more CRH-R1 antagonists and/or CRH-R2 agonists comprised in one of more individual pharmaceutical compositions (claim 13).

Wei et al. teach synthetic D-amino acid-substituted peptides with selective CRH-R2 agonist activity (see whole document, for example, abstract; p. 1187, Table 2; p. 1189, right column, last paragraph). Possible therapeutic applications are discussed at p. 1184, right column, 1st paragraph, thus the usage taught in Wei et al. is not inconsistent with pharmaceutical usage of claim 4 and its dependents. In addition, Wei et al. teach that the synthetic peptides were dissolved and diluted in sterile saline or incubation medium (for in vitro studies) at p. 1186, left column, 1st paragraph, thus meeting the limitations of claim 6. In addition, Wei et al. teach that the formulations were injected (see p. 1185, left column, 2nd paragraph), thus meeting the limitations of claims 5, which recites systemic administration and 7, which recites parenteral administration (i.e., taken into the body in a manner other than through the digestive tract, as by intravenous or intramuscular injection) and 8, which recites that the composition is formulated as an injection liquid. Finally, because Wei et al. teach administration of measured amounts (for example Table 2, Figures 2-5), the limitations of claim 13 (kit) is also met. Thus claims 4-8 and 13 are anticipated by Wei et al.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00am - 2:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

/Elizabeth C. Kemmerer/
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